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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,445	10/18/2001	Amparo Cano Garcia	0380-P02492U	1538

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/806,445	Applicant(s) CANO GARCIA ET AL.	
	Examiner Misook Yu	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 13-21* is/are pending in the application.

4a) Of the above claim(s) *1,6-8 and 13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group 2, method of cancer diagnosis using Snail (new claims 18-21) in Paper No. 11 is acknowledged.

Claims 1, 6-8, and 13-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claims 2-5 are cancelled. Claims 1, 6-8, and 13-21 are pending. Claims 18-21 are examined on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitations "the determination" in line 1and "the invasive and metastatic capacity" in lines 1 and 2, the limitations "the presence" in line 6. There is insufficient antecedent basis for these limitations in the claim.

Claim 18 recites "compound" but is not clear what the metes and bounds are for compound.

For the purpose of this office action, this examiner will assume "compound" means "comprising". However, this treatment does not relieve applicant a burden of responding this rejection.

Claims 18-21 are indefinite because claims 18-21 recite the phrase "metastatic capacity". It is unclear what is meant by "metastatic capacity" or what parameters of metastatic capacity are being claimed for patent protection, is the metastatic capacity of the tumor established by (1) the ability of the cells to detach from monolayers, (2)

resistance to lysis by lymphocytes, (3) resistance to lectin-mediated toxicity, (4) attachment to collagen, (5) the ability to invade various tissues maintained in organ culture, or (6) a combination of these parameters? Or does metastatic capacity mean something else for the invention disclosed in the instant application? The specification does not define a boundary of "metastatic capacity".

Claim 19 recites the limitation "the step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites the limitation "the step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 21 recites the limitation "the step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 20 and 21 recite "a generic precursor" but it is not clear what the metes and bounds are for "a generic precursor".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 18-21 are drawn to method for determination of an invasive ***and*** metastatic capacity of an epithelial tumor. The specification in figure legend of Figure 6 at page 10 lines 5-17 and Cano et al (a references cited in PCT/ES00/00226, Feb. 2000, Nature Cell Biology 2, 67-82) at Fig. 7 (I) teach that mouse Snail mRNA expression is observed only in the undifferentiated invasive area of chemically induced mouse tumor, not in the undifferentiated invasive area of the tumors induced by PDV or CarB. However, neither the specification nor any art of record teaches a relationship between metastatic capacity of a tumor and expression of Snail. There is no indication that Snail expression seen in Figure 6 (I) in invasive area of

chemically induced tumor in nude mouse could be correlated with metastatic capacity *in vivo* tumor. Further, although it is known in the art that assays for human cancer cell invasion and metastasis exist (see Frandsen et al., Fibrinolysis, 1992:6, Suppl 4:71-76), the specification does not present any data on a relationship between Snail and metastatic potential of an epithelial tumor. Hill (The Basic Science of Oncology, Tannock et al., Eds, McGraw Hill, NY, 1992, pp 178-195) specifically teaches that primary tumors contain populations of cells with different metastatic abilities. The development of metastatic potential may be viewed as one of the late states of a process that has been in progress since the initiation of the tumor and that results in the evolution of populations of tumor cells which become more growth autonomous and malignant, thus determination of metastatic potential is dependent upon stage of tumor development and metastasis involves complexity of the processes and it is particularly difficult to distinguish tumors that are likely to metastasize (see the Summary at p. 193). Further, conventional assays of metastatic capacity test not only invasive properties, but also properties of the ability of cells to invade into and out of blood vessels, to survive in circulation, to arrest and to grow at a new site, for example, metastatic capacity is tested in model systems such as chorioallantoic membranes in chicken eggs. A small window is made in the shell of the eggs, sample cells are introduced to the membrane, invasion of the cells across membrane is observed microscopically and the formation of metastases in organs of the chick embryo can be quantitated (Hill, cited supra, p. 184, para 4).

The specification does not take into account the other processes required for metastasis and does not demonstrate a relationship between expression of Snail and metastatic capacity. Without further guidance or exemplification on expression of Snail on metastatic capacity of tumors, the use of a method for determining metastatic capacity of a tumor of epithelial cell origin comprising determining a presence of Snail in a biological sample wherein the presence of Snail is characteristic of an invasive and metastatic capacity of an epithelial tumor would be highly unpredictable since it has not been demonstrated that presence of Snail is indicator of the invasive and metastatic capacity of a epithelial tumor. The specification fails to provide sufficient guidance to

enable one skilled in the art to use a method for determining an invasive and metastatic capacity of a tumor of epithelial cell origin comprising determining a presence of a marker, Snail in a biological sample wherein the presence of said marker in said tumor cells indicates the invasive and metastatic capacity in said epithelial tumor cells. The specification gives no guidance for or exemplification of a method for determination of an invasive and metastatic capacity of a tumor of epithelial cell origin by determining presence of a marker, Snail in a biological sample and comparing that sample to a sample of normal cells. In view of the unpredictability in the art pertaining to the presence of Snail on metastasis of any tumors and that a relationship between metastatic capacity of a tumor and altered expression of Snail is not known in the art as discussed above as well as the lack of sufficient guidance in the specification, one skilled in the art would be forced into undue experimentation in order to use the invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 18 and 19 are drawn to method for determination of an invasive ***and*** metastatic capacity of an epithelial tumor by determining a presence of Snail protein using ant-Snail antibodies that binds to the Snail protein. The specification fails to teach: 1) if Snail protein is expressed in any tumor; 2) how to make or where to obtain mouse anti-Snail antibodies; 3) how to make or where to obtain human anti-Snail antibodies. As for the issues 1) and 2) above the Snail expression in Figure 5 and 6 (mRNA expression data presented in these figures) of the instant specification does not give any information about expression of Snail protein because expression level of mRNA does not necessarily correlates with expression level of a protein in the same cells. The level of translation of mRNA is not predictable because the there are a multitude of homeostatic factors affecting translation of the mRNA into proteins. Fu et al. (The EMBO Journal 15, 4392-4401Abstract only) teaches that expression of p53 protein is not correlated with the expression of mRNA (see the abstract only). As for the issue 3) above the instant

specification or any art of record fails to teach that the identity of human Snail protein is known at the time of the instant application although Smith et al (1992, Development 116, 1033-1039) teach in Fig. 1 that mouse Snail, alias Sna was cloned and the entire protein sequence is known. Considering that the specification does provide any guidance or examples concerning the three issues raised above, unpredictability in the art using Snail as marker for invasive and metastatic capacity of a tumor, it is concluded that undue experimentation is required for one skilled in art to practice the invention.

Claims 18, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 18 and 19 are drawn to method for determination of an invasive ***and*** metastatic capacity of an epithelial tumor by determining a presence of Snail expression using either in situ hybridization or RT-PCR. The specification in figure legend of Figure 6 at page 10 lines 5-17 teaches that mouse Snail mRNA expression is observed only in the undifferentiated invasive area of chemically induced mouse tumor, not in the undifferentiated invasive area of the tumors induced by PDV or CarB. However, the specification fails to teach what kinds of probe could be used to detect the expression in Figure 6. What are the nucleotide sequences of the probes? How long are they? What are actual method steps and procedures involved in Figure 6? Considering limited guidance in the specification and unpredictability in the art using Snail as marker for invasive and metastatic capacity of a tumor, it is concluded that undue experimentation is required for one skilled in art to practice the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome above 112, first paragraph rejections of claims 18, 20, and 21, claims 18, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Snail expression as a marker ***only in undifferentiated invasive areas of chemically induced mouse tumor***, does not reasonably provide enablement for Snail expression to be used as an

invasive and metastastic capacity of an epithelial tumor caused by any other method . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claims 18 20, and 21 are drawn to method for determination of an invasive ***and*** metastatic capacity of an epithelial tumor by determining a presence of Snail expression using in situ hybridization or RT-PCR. The specification in figure legend of Figure 6 at page 10 lines 5-17 and Cano et al (a references cited in PCT/ES00/00226, Feb. 2000) at Fig. 7 (I) teach that mouse Snail mRNA expression is observed only in the undifferentiated invasive area of chemically induced mouse tumor, ***not in the undifferentiated invasive area of the tumors induced by PDV or CarB***. In view of the unpredictability in the art pertaining to the presence of Snail for invasive and metastastic capacity of any tumor, a relationship between metastatic capacity of a tumor and altered expression of Snail is not known in the art as discussed above as well as the lack of sufficient guidance and example in the specification, it is concluded that undue experimentation is necessary for one of skilled in the art to use the invention commensurate in scope with these claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
June 30, 2002

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